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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A 3058	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/10064	International filing date *(day/month/year)* 10.09.2003	Priority date *(day/month/year)* 10.09.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/28		
Applicant AFFIMED THERAPEUTICS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.03.2004	26.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Alconada Rodríguez, Telephone No. +49 30 25901-326

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10064

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-17 received on 04.10.2004 with letter of 01.10.2004

Drawings, Sheets

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

7. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Statement

Novelty (N)	Yes:	Claims	11,16,17
	No:	Claims	1-10, 12-15
Inventive step (IS)	Yes:	Claims	11
	No:	Claims	1-10, 12-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99/57150 A (DEUTSCHES KREBSFORSCH ;KIPRIYANOV SERGEJ (DE); LITTLE MELVYN (DE)) 11 November 1999 (1999-11-11)

D2: KIPRIYANOV S M ET AL: "Two amino acid mutations in an anti-human CD3 single chain Fv antibody fragment that affect the yield on bacterial secretion but not the affinity" PROTEIN ENGINEERING 1997 UNITED KINGDOM, vol. 10, no. 4, 1997, pages 445-453, XP002237690 ISSN: 0269-2139

D3: MOTTRAM P L ET AL: "NEW ANTI-CD3 AGENTS FOR TRANSPLANTATION TOLERANCE INDUCTION" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 23, no. 10, 1998, pages 1091-1098, XP000918108 ISSN: 0377-8282

D4: EP-A-0 952 218 (HOECHST MARION ROUSSEL DE GMBH) 27 October 1999 (1999-10-27)

1. Document D1 provides divalent and tetravalent antibodies which are specific for - CD19 and CD3 and which consist of the VH and VL regions from the CD19-specific HD37 hybridoma and from the CD3-specific OKT3 hybridoma (see example 1). CD19/CD3 diabodies are obtained by placing the VH and VL chains according to the arrangement shown in figure 1 (VHA-VLB-VHA-VLA), wherein the VH and VL chains are connected via a peptide linker having the sequence SAKTTPKLGG (see figure 5, amino acids at positions 141-150 and 412-421). The document provides nucleic acid sequences which code for the bivalent and tetravalent Fv constructs (see page 4, second paragraph), vectors comprising said polynucleotides suitable for expression in bacterial (see example 3) and yeast (see example 4) cells and the use of said antibody for therapeutic purposes, in particular, as a cytotoxic reagent against CD19-positive Raji Burkitt lymphoma cells (see paragraph bridging pages 4 and 5, example 5 and claim 21). In view of the teaching in this document, **claims 1-6, 9, 10 and 12-15** lack novelty. The objection against claim 6 results from the fact that the antibody produced by the ATCC deposit number CRL 8001 is the OKT3 mAb, which is the same used in document D1.

2. It could be argued that the claimed antibodies differs from those provided in D1 because they are capable of suppressing an immune reaction, whereas it has not been proven that any of the antibodies disclosed in D1 shows this function. The IPEA can not follow the argument for the following reason. The ability of the claimed antibodies to suppress an immune reaction is an intrinsic property of the claimed compounds, which depends exclusively on the down-regulation of CD3 molecules from the surface of T-cells which is caused by the anti-CD3 binding regions within the antibody. This implies that every compound known in the art having the same structural features as the claimed compounds will also show the same functional activities, irrespective of whether these activities have been tested. Furthermore, the inclusion in the claim of a feature which relates to the alleged function of the claimed compounds can not serve to restore novelty of said compounds over the prior art compounds when both groups of compounds are structurally indistinguishable. The broad wording used in the claim includes not only the multivalent antibodies wherein all the valencies are specific for CD3, as the examples of the present application provide, but also those diabodies as shown in D1 of dual specificity which contain VH and VL regions specific for two different polypeptides. Thus, in the absence of a specific limitation in the claim to those antibodies which contain only anti-CD3 binding regions, the subject-matter of the claim is anticipated by D1.

3. The antibodies containing a substitution in cysteine at position H100A (**claims 7 and 8**) lack an inventive step. The substitution is known from D2 as improving the stability of the ScFV molecule, so it would be obvious for the skilled person to use the same mutation in order to improve the stability of antibodies which consists of several tandemly-arranged ScFv molecules

4. Claim 11 relates to the vector pSKK3-scFv_6-anti-CD3 deposited under the accession number DSM15137. This vector consists of six scFv molecules arranged in tandem, wherein all the scFv molecules contain the VH and VI regions of the OKT3 mAb specific for CD3. The plasmid has not been disclosed in the prior art. In addition, none of the prior documents provide any indication tat would allow the skilled person to arrive to such an antibody and therefore, the subject-matter of claim 11 and all related claims is new and involves an inventive step.

5. The use of the recombinant antibodies of the invention for the treatment of acute transplant rejection (claim 16) does not involve an inventive step. Document D3,

which can be considered as the closest prior art, discloses the use of an anti-CD3 mAbs obtained from the OKT3 hybridoma and immunoconjugates thereof coupled to a cytotoxic drug as reagents suitable to prevent organ transplant rejection, whereas both the antibodies as such as well as the antibodies coupled to idarubicin are able to prolong survival of a heart allograft, which suggests that the mAbs has an immunosuppressive activity of its own and that the presence of a toxin is not absolutely necessary to achieve said activity (page 1092, left-hand column, first paragraph and page 1094, right-hand column, last paragraph to page 1096, left-hand column, second paragraph and table III). The present application differs from the teaching of D3 in that the antibodies used for the prevention of transplant rejection are anti-CD3 bivalent antibodies which are devoid of constant antibody regions. Thus, the problem to be solved by the present application can be summarised as the provision of alternative anti-CD3 antibodies. The skilled person, when confronted with the problem of providing alternative anti-CD3 antibodies and knowing that said antibodies are capable to prolong survival of a grafted organ (i.e. they reduce transplant rejections) on their own, would attempt to use other anti-CD3 molecules known in the art as immunotherapeutic reagents, thus considering the antibodies provided in D1 and arriving at the subject-matter of **claim 16**, as far as it relates to the polynucleotide of claim 9 or the expression vector of claim 10, without the exercise of any inventive skills.

6. Pharmaceutical compositions comprising nucleic acid sequences coding for bivalent antibodies and the uses thereof for gene therapy are known from D4 (see paragraph [0054] and claims 35 and 37). Thus, no inventive step can be acknowledged for the use of nucleic acid encoding the bivalent anti-CD3 antibodies for gene therapy as defined in **claims 14, 15 and 17**.

Amended Claims

(1-Oct-04)

1. A bivalent or multivalent antibody characterized by the following features:

(a) it is capable of supressing an immune reaction;

(b) it is devoid of constant antibody regions; and

(c) it binds an epitope on the CD3 complex of the T-cell receptor.

2. The antibody of claim 1 that is a diabody.

3. The antibody of claim 1 that comprises two scFv antibodies linked by a peptide linker.

4. The antibody of claim 1 that is a single chain diabody.

5. The antibody according to any one of claims 1 to 4, wherein the variable V_H and V_L domains are connected via the peptide linker SAKTTP or SAKTTPKLGG.

6. The antibody according to any one of claims 1 to 5 wherein the variable domains correspond to the variable domains of the antibody produced by the hybridoma of ATCC deposit number CRL 8001.

7. The antibody according to claim 6, wherein a cysteine at position H100A (Kabat numbering system) has been exchanged for another amino acid.

8. The antibody according to claim 7, wherein the cysteine has been exchanged for a serine.

9. A polynucleotide, which encodes an antibody of any one of claims 1 to 8.

AMENDED SHEET

10. An expression vector comprising the polynucleotide of claim 9.

11. The expression vector of claim 10, which is pSKK3-scFv_6-anti-CD3 (DSM 15137).

12. A host cell containing the expression vector of claim 10 or 11.

13. A pharmaceutical composition containing the antibody of any one of claims 1 to 8, the polynucleotide of claim 9 or the expression vector of claim 10 or 11.

14. Use of an antibody which is characterized by the following features:

(a) it is capable of supressing an immune reaction;

(b) it is devoid of constant antibody regions; and

(c) it binds an epitope on the CD3 complex of the T-cell receptor; or the polynucleotide of claim 9 or the expression vector of claim 10 or 11 for the preparation of a pharmaceutical composition for immunotherapy.

15. Use according to claim 14, wherein the antibody is the antibody of any one of claims 1 to 8.

16. Use according to claim 14 or 15, wherein said immunotherapy is a therapy against acute transplant rejections.

17. Use of the polynucleotide of claim 9 or the expression vector of claim 10 or 11 for the preparation of a pharmaceutical composition for gene therapy.

AMENDED SHEET